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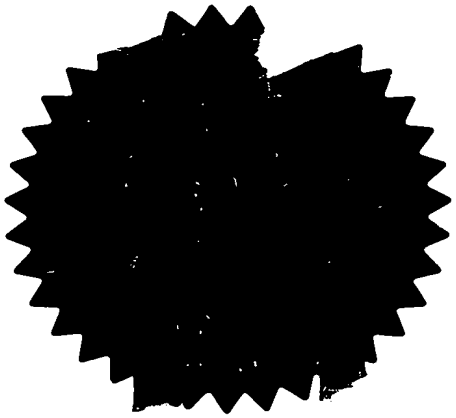

Signed R. Mahoney

Dated 24.1.01.

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1. Your reference

P/663

2. Patent application number
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9816899.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

THE BOOTS COMPANY PLC
1 THANE ROAD WEST
NOTTINGHAM
NG2 3AA

Patents ADP number *(if you know it)*

884692001

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)*

MRS E J SMITH

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

THERAPEUTIC AGENTS

This invention relates to pharmaceutical compositions comprising an ibuprofen medicament and a domperidone medicament.

Ibuprofen, namely 2-(4-isobutylphenyl)propionic acid, is a well known medicament with analgesic, anti-inflammatory and anti-pyretic properties. It is usually sold in the form of racemic ibuprofen (equal amounts of the S(+)-ibuprofen and R(-)-ibuprofen enantiomers). It may also be in the form of the purified form of either enantiomer, especially S(+)-ibuprofen which is acknowledged to be the active form of racemic ibuprofen. Ibuprofen is also available in salt form, for example the sodium or lysine salt of ibuprofen. Ibuprofen is available under prescription (eg Brufen (RTM)), primarily for the treatment of painful and anti-inflammatory disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, postoperative pain, post partum pain and soft tissue injuries, generally at doses up to 3200 mg per day. Ibuprofen is also available as a non-prescription drug (eg Nurofen (RTM)), primarily for the treatment of symptoms of pain and fever including headache, migraine, rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea, dental pain and colds and flu, generally at doses up to 1200mg per day.. The commercially available ibuprofen tablets usually contain 200mg, 400 mg, 600 mg or 800 mg racemic ibuprofen. When an enantiomer or salt of ibuprofen is used the amount of active substance present may be such that the same therapeutic effect is obtained as from the presently-available doses of racemic ibuprofen. Hereinafter the term "ibuprofen" means any enantiomer of ibuprofen or mixtures of enantiomers including the racemic mixture.

Domperidone, namely 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one is a well known medicament with antiemetic properties. Domperidone is available

which have cohesive properties to bind the combination of ingredients are important in formulating solid compositions. Further useful excipients are disintegrating agents, which, when exposed to the aqueous medium after ingestion, cause the solid composition to release the active ingredient at a desired rate, for example substantially immediately or at a desired controlled rate. There may also be provided carrier materials which allow the homogeneous mixing of the active ingredients throughout the dosage form and which may aid compressibility of the tablets. Many such carrier materials have disintegrating properties and/or cohesive properties when used in certain proportions in the dosage form. Many other excipients may also be added to provide appropriate release and absorption into the body.

In the production of solid dosage forms there is often a pre-granulation stage in which the active ingredient is combined with an inert excipient and formed into a free-flowing, homogeneous granular composition which is capable of being mixed with other ingredients and formed into a solid dosage form. In this pre-granulation stage, most commonly the powdered ingredients are mixed and then granulated with a granulating fluid (eg water or a pharmaceutically acceptable organic solvent such as an alcoholic solvent) to form a granular composition. A granulating agent which may be a solid and which further imparts cohesive properties to the granule may be present, either dissolved in the granulating liquid or mixed in with the powdered ingredients. Water-soluble polyvinylpyrrolidone is a preferred granulating agent as it is readily soluble both in water and in alcoholic solvents and it provides good cohesive properties to the resulting granule. Polyvinyl pyrrolidone has been used previously in providing both granular compositions of ibuprofen and granular compositions of domperidone. Water-soluble polyvinylpyrrolidone is of value in the manufacturing process because it allows changes in the composition of the granulating fluid (eg water may replace the alcoholic solvent or they may be combined in a desired proportion) without affecting the solid ingredients in the composition. Such changes in the granulating fluid may be necessary to

ingredients are discussed therein including solid compositions for oral administration, liquid fill compositions and oral liquid compositions, compositions for topical administration, rectal administration and parenteral administration and also spray formulations. Some solid compositions are disclosed therein which may comprise a diluent, a lubricating agent, a disintegrating agent and optionally a binder and/or a flow aid. The preferred binder (which reflects the state of the art as given above) is said to be polyvinylpyrrolidone and this is reflected by its use as an excipient in a number of illustrative solid compositions. The compositions specifically disclosed in the Examples therein are excluded from the scope of the present patent application. These may be considered as:-

(a) compositions wherein the carrier comprises a mixture of 15-38% by weight maize starch or 9-11% by weight microcrystalline cellulose in combination with a starch component comprising 3-6% by weight dried maize starch or 6-10% by weight pregelled starch;

(b) tablets formed by direct compression containing 9-11% by weight microcrystalline cellulose and 5-6% by weight lactose.

The ibuprofen molecule exists in two enantiomeric forms and the term ibuprofen medicament as used herein is intended to embrace the individual enantiomers, especially S(+)-ibuprofen, and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as racemic ibuprofen. The ibuprofen medicament may be also present in the form of any salt or other derivative of ibuprofen or its enantiomers. If necessary, the ibuprofen medicament may comprise one or more ibuprofen active ingredients such as racemic ibuprofen and S(+)-ibuprofen in combination. However, we prefer that the ibuprofen medicament comprises a single ibuprofen active ingredient. Representative examples of salts of racemic or S(+)-ibuprofen include alkali metal salts, for example the sodium or potassium salts of ibuprofen; alkaline

1-10% and more preferably 1-5% by weight of the composition. Unit dosages may comprise the domperidone medicament to an extent of 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 40mg and 50mg. Suitably the pharmaceutical compositions are administered in divided doses throughout the day so the amount of domperidone (or the corresponding amount of a salt thereof) to be administered at each dosing time is 5 to 50mg (preferably 5 to 25mg, more preferably 5 to 20mg). Therefore, if two dosage forms are to be administered at each time, the dosage forms should contain 2.5 to 25mg, (preferably 2.5 to 12.5mg, more preferably 2.5 to 10mg) domperidone medicament.

Preferred forms of the composition are as granular compositions or as dosage forms. A unit dosage form preferably contains one or two dosage forms, preferably tablets.

The carrier suitably forms up to 65% by weight of the dosage form. Preferred dosage forms include 20-60% by weight carrier, more preferably 25-60% by weight and most preferably 30-50%. The carrier is adapted to combine the components to form a stable solid composition.

The carrier comprises at least one inert diluent material. Examples of inert diluent materials include one or more of a sugar material (including sugar alcohols) (eg dextrose, lactose, sucrose, compressible sugar, mannitol and sorbitol), calcium carbonate, calcium sulphate, dextrates, dextrin, dicalcium phosphate, glyceryl palmitostearate, hydrogenated vegetable oil (type I), kaolin, magnesium carbonate, magnesium oxide, maltodextrin, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, hydroxypropylmethyl cellulose, pregelatinised starch, sodium chloride, starches (eg wheat starch, maize starch, potato starch, rice starch, tapioca starch) and modified starches and tricalcium phosphate. Preferred diluents have good cohesive properties and serve to bind the materials together. Further preferred diluents are compressible and include microcrystalline cellulose,

The composition may also include further ingredients. These ingredients will be used in the composition in an amount as used by the person skilled in the art. These may include a flow aid, such as talc or colloidal silicon dioxide which may preferably be used up to an extent of 4% by weight of the composition, for example 0.5-2.0% by weight of the composition. Lubricants such as stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, hydrogenated cotton seed oil, calcium stearate, sodium stearyl fumarate or magnesium stearate or mixtures thereof may also be included in the composition. These may be used to an extent of up to 4% by weight of the dosage form, for example 0.5-2% by weight of the composition. Anti-adherents such as talc may further be included in an amount of up to 4% by weight of the composition. For example, 0.5-2% by weight of the composition.

Most commonly, the components will be compressed into tablets in a solid composition according to the present invention. Thus, the carrier is capable of being compressed with the active ingredients to form a robust tablet with cohesive properties. The tabletting process may contain a granulation stage in which at least one of the active ingredients and at least a portion of the diluent is mixed with a granulating fluid, either in the presence or absence of a granulating agent and formed into a granular composition which has sufficient free-flowing and cohesive properties to be capable of further processing with other excipients and compressed into a tablet. The granulation stage may also be carried out under dry conditions, ie in the absence of a granulating fluid.

Thus, in a preferred aspect of the present invention, there is provided a solid pharmaceutical composition formed by compressing a granular composition comprising:-

(a) an ibuprofen medicament;

(b) a domperidone medicament;

(c) a carrier comprising at least one diluent combined with at least one disintegrating agent and a granulating agent said carrier being adapted to combine the ingredients in a stable composition

characterised in that the granulating agent is selected from a polymeric material granulating agent and a sugar material granulating agent and is substantially free of water-soluble polyvinyl pyrrolidone.

Thus, preferably the composition further comprises a granulating agent. The term "granulating agent" and "binding agent" herein are used interchangeably. A wet granulation process is particularly preferred, where the granulating agent imparts cohesive properties to the powdered materials. Preferably the solid compositions according to the present invention are produced by a process including a wet pre-granulation stage in the presence of a granulating fluid and a granulating agent. The granulating agent may be a solid; it may be present as a solid powder material or it may be dissolved in the granulating fluid. The granulating agent is preferably selected from a polymeric material, eg a natural or synthetic gum, and a sugar material. Examples of granulating agents or binders include acacia, alginic acid, carbomer, carboxymethyl cellulose sodium, dextrin, alkyl celluloses such as methylcellulose and ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil (type I), hydroxyalkyl celluloses such as hydroxyethylcellose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, liquid glucose, magnesium aluminium silicate, maltodextrin, methylcellulose, polymethyacrylates, pregelatinised starch, sodium alginate, starch (eg wheat starch, maize starch, potato starch, rice starch, tapioca starch), modified starch, sucrose and zein or mixtures thereof. Preferred polymer materials are cellulose materials as listed above, particularly hydroxypropyl cellulose and hydroxypropymethyl cellulose. These ingredients will be used in the composition in an amount as used by the person skilled in the art. This will generally be in the range of up to 10% by weight, or preferably 0.5-5% by weight and most preferably 2-4%.

liquid prior to ingestion), suppositories or inserts and buccal or sub-lingual tablets. In the compression process the tablets are generally formed by a wet granulation, a dry granulation or a direct compression process. In these processes the ingredients are combined as desired, either to form a homogeneous blend which is then compressed into a tablet or to make different blends which are then compressed to make different layers in a tablet. In the wet granulation process, one or both of the active ingredients is homogeneously blended with at least a portion of the carrier and formed into granules by the addition of a granulating fluid preferably in the presence of a granulating agent. Preferably both the ibuprofen medicament and the domperidone medicament are included in the granular product. The granulating agent may be added to (preferably dissolved in) the granulating fluid prior to addition to the blend of active ingredient and carrier or the granulating agent may be blended with the active ingredient and carrier prior to the addition of the granulating fluid. The granulating fluid may be water or an organic solvent, eg a C_{1-6} alkanol such as ethanol, propan-1-ol or propan-2-ol or a mixture thereof. The granulated material is then dried, sieved, added to other ingredients as necessary and blended to form a homogeneous mixture prior to compression into tablets. In the dry granulation process, the ingredients are formed into granules in the absence of a liquid, such as by roller compaction or slugging. The granules are then mixed with the remaining ingredients and compressed into a solid dosage form. The compositions according to the present invention may also be formed by sieving powdered ingredients into a container and then blending to form a homogeneous mixture. The mixture may be directly compressed into tablets. The "direct compression" process does not include a pre-granulation step. The ingredients are combined to form a homogeneous mixture and then fed to a tabletting for compression into tablets.

In a preferred process, the composition is formed by a process including a wet granulation stage as described above. Desirably, both the active ingredients are present in the granular product together with an inert diluent and

Corporation under the trade name Ac-Di-Sol; Hydrogenated cotton seed oil is available from Edward Mendell under the trade name Lubritab; Hydroxy propylmethyl cellulose is available from the Dow Corporation under the trade name Methocel 50. Hydroxypropyl cellulose is available from the Dow Corporation under the trade name Klucel LF; Colloidal silicon dioxide is available from Degussa under the tradename Aerosil 300.

Examples 1 to 3

Ingredient	Example 1	Example 2	Example 3
Ibuprofen	60.5%	60.5%	59.7%
Domperidone Maleate	1.9%	1.9%	1.9%
Microcrystalline cellulose	6.1%	6.1%	-
Croscarmellose sodium	9.7%	9.7%	3.0%
Magnesium stearate	0.6%	-	0.6%
Hydrogenated cotton seed oil	-	0.6%	-
Tricalcium phosphate	18.2%	18.2%	-
Hydroxypropyl cellulose	3.0%	-	-
Hydroxypropylmethyl cellulose	-	3.0%	-
Colloidal silicon dioxide	-	-	0.6%
Sorbitol	-	-	34.2%

The composition of Example 1 was prepared according to the following steps:-

(a) the ibuprofen, domperidone maleate, tricalcium phosphate, hydroxypropyl cellulose, croscarmellose sodium and microcrystalline cellulose were sieved and blended to form a homogeneous mixture;

(b) the mixture was granulated to a suitable end point with water and dried;

Example 4 was prepared in a similar manner as described in Example 1 except that hydroxypropylmethyl cellulose replaced hydroxypropyl cellulose in stage (a) as the granulating agent and stearic acid replaced magnesium stearate as lubricant in stage (c).

Example 5 was prepared in a similar manner as described in Example 1 except that no granulating agent was present in stage (a), isopropanol was used as the granulating fluid in stage (b) and stearic acid replaced magnesium stearate as lubricant in stage (c).

Example 6 was prepared in a similar manner as described in Example 1 except that hydroxypropylmethyl cellulose replaced hydroxypropyl cellulose in stage (a) as granulating agent.

Example 7

Ingredient	% w/w
Ibuprofen	59.8%
Domperidone	1.9%
Colloidal silicon dioxide	0.2%
Magnesium stearate	0.6%
Lactose	9.2%
Microcrystalline cellulose	22.9%
Sodium lauryl sulphate	1.9%
Sodium starch glycolate	3.5%

The composition of Example 7 was prepared by sieving and blending all the above powdered ingredients to form a homogeneous mixture and compressing to form tablet cores containing 200mg of ibuprofen and 10mg equivalent of

CLAIMS

1. A solid pharmaceutical composition comprising:-

(a) an ibuprofen medicament;

(b) a domperidone medicament; and

(c) a carrier comprising diluent combined with a disintegrating agent;

characterised in that the carrier is substantially free of water-soluble polyvinyl pyrrolidone.
excluding the compositions disclosed in the Examples of PCT/EP98/00649

2. A solid pharmaceutical composition comprising:-

(a) an ibuprofen medicament;

(b) a domperidone medicament; and

(c) a carrier comprising diluent combined with a disintegrating agent;

characterised in that the carrier is substantially free of water-soluble polyvinyl pyrrolidone,

excluding

(a) compositions wherein the carrier comprises a mixture of 15-38% by weight maize starch or 9-11% microcrystalline cellulose in combination with a starch

characterised in that the granulating agent is selected from a polymeric material granulating agent and a sugar material granulating agent and is substantially free of water-soluble polyvinyl pyrrolidone.

5. A process to prepare a solid composition according to any one of claims 1 to 4 comprising combining the excipients and formulating into a solid composition.

6. The use of a composition according to any one of claims 1 to 4 to treat migraine and other painful conditions having symptoms of nausea and dyspepsia